EXHIBIT A174

JAMA | Original Investigation

Effect of Aclidinium Bromide on Major Cardiovascular Events and Exacerbations in High-Risk Patients With Chronic Obstructive Pulmonary Disease

The ASCENT-COPD Randomized Clinical Trial

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Supplemental content

IMPORTANCE There is concern that long-acting muscarinic antagonists increase cardiovascular morbidity or mortality in patients with chronic obstructive pulmonary disease (COPD).

OBJECTIVE To determine the cardiovascular safety (noninferiority) and efficacy (superiority) of aclidinium bromide, 400 μg twice daily, in patients with COPD and cardiovascular disease or risk factors.

DESIGN, SETTING, AND PARTICIPANTS Multicenter, randomized, placebo-controlled, double-blind, parallel-design study conducted at 522 sites in North America. A total of 3630 patients with moderate to very severe COPD and either a history of cardiovascular disease or at least 2 atherothrombotic risk factors were randomized; follow-up occurred for up to 3 years until at least 122 major adverse cardiovascular events (MACE) occurred. The first patient was enrolled on October 16, 2013 and the last on August 22, 2016. The final patient completed follow-up on September 21, 2017.

INTERVENTIONS Patients were randomized to receive aclidinium (n = 1812) or placebo (n = 1818) by dry-powder inhaler, twice daily for up to 3 years.

MAIN OUTCOMES AND MEASURES The primary safety end point was time to first MACE over up to 3 years (hazard ratio [HR] 1-sided 97.5% CI noninferiority margin = 1.8). The primary efficacy end point was the annual COPD exacerbation rate during the first year of treatment. Secondary outcomes included an expanded MACE definition (time to first MACE or serious cardiovascular event of interest) and annual rate of exacerbations requiring hospitalization.

RESULTS Among 3589 patients analyzed (mean age, 67.2 years; 58.7% male), 2537 (70.7%) completed the study. Of these, 69 (3.9%) aclidinium and 76 (4.2%) placebo patients had a MACE (HR, 0.89; 1-sided 97.5% CI, 0-1.23); the expanded MACE definition included 168 (9.4%) aclidinium vs 160 (8.9%) placebo patients with events (HR, 1.03; 1-sided 97.5% CI, 0-1.28). Annual moderate to severe exacerbation rates (aclidinium, 0.44; placebo, 0.57; rate ratio, 0.78; 2-sided 95% CI, 0.68-0.89; $P < .001$) and rate of exacerbations requiring hospitalization (aclidinium, 0.07; placebo, 0.10; rate ratio, 0.65; 2-sided 95% CI, 0.48-0.89; $P = .006$) decreased significantly with aclidinium vs placebo. The most common adverse events were pneumonia (aclidinium, 109 events [6.1%]; placebo, 105 events [5.8%]), urinary tract infection (aclidinium, 93 events [5.2%]; placebo, 89 events [5.0%]), and upper respiratory tract infection (aclidinium, 86 events [4.8%]; placebo, 101 events [5.6%]).

CONCLUSIONS AND RELEVANCE Among patients with COPD and increased cardiovascular risk, aclidinium was noninferior to placebo for risk of MACE over 3 years. The rate of moderate to severe COPD exacerbations was reduced over the first year.

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Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality worldwide.[1] It is associated with increased risk of cardiovascular morbidity,[2] with approximately one-third of COPD deaths being due to cardiovascular disease.[3,4] Although long-acting muscarinic antagonists (LAMAs) are widely used for maintenance bronchodilation in patients with COPD, there is controversy surrounding their cardiovascular safety.[5-11]

Several meta-analyses and epidemiological studies have demonstrated an increased risk of cardiovascular events following treatment with either short-acting muscarinic antagonists (SAMAs) or LAMAs.[5,8-10] In contrast, large-scale clinical trials of the LAMA tiotropium have not demonstrated an increase in major adverse cardiovascular events (MACE; a composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke),[6,11,12] and the US Food and Drug Administration has concluded that current data do not support an increased risk of stroke, myocardial infarction, or death associated with tiotropium in patients with COPD.[7] This discrepancy can be explained in part because patients with significant cardiovascular disease are typically excluded from clinical trials such as the UPLIFT study.[6]

Short-term studies of aclidinium have demonstrated decreased annual rates of exacerbation compared with placebo after 3 to 6 months of treatment,[13] but this has not been established beyond 6 months. Given this background, the dual objectives of the current trial were to evaluate the effects of aclidinium bromide, 400 μg twice daily, on MACE (noninferiority to placebo) and COPD exacerbations (superiority to placebo) in patients with COPD and a history of cardiovascular disease or cardiac risk factors.[14]

Key Points

Question In patients with chronic obstructive pulmonary disease (COPD) and also with increased cardiovascular risk, does aclidinium bromide, 400 μg twice daily, increase major adverse cardiovascular events (MACE) and decrease COPD exacerbations?

Findings In this randomized study of 3589 patients with COPD and also with increased cardiovascular risk, the estimated MACE hazard ratio (aclidinium vs placebo) was 0.89 over 3 years; the 1-sided 97.5% CI of 1.23 did not exceed the noninferiority margin of 1.8. For moderate to severe COPD exacerbations, the estimated rate ratio (aclidinium vs placebo) was 0.78 during the first year and was statistically significant.

Meaning Aclidinium, compared with placebo, reduced COPD exacerbations and did not result in an inferior risk of MACE.

Methods

Study Design

The study design and methods of the ASCENT-COPD trial are available in Supplement 1.[14] In brief, this was a phase IV, multicenter, double-blind, randomized, placebo-controlled, parallel-group noninferiority study conducted at 522 sites in the United States and Canada (eFigure 1 in Supplement 1).[14] The study comprised a 2-week washout/run-in period followed by a double-blind treatment phase, during which patients were randomized 1:1 to receive aclidinium, 400 μg, or matching placebo twice daily from a multidose dry-powder inhaler (Genuair/Pressair; AstraZeneca) for up to 36 months. This was an event-driven trial that was planned to terminate on the date that at least 122 patients were projected to have experienced an adjudicated MACE. Each patient was exposed to aclidinium or matching placebo for a maximum of 3 years. The trial protocol (see Supplement 2 and statistical analysis plan in Supplement 3) and informed consent procedures were approved by the institutional review board with controlling authority at each study site. All patients provided written informed consent prior to the conduct of any study-specific procedures. The study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines.

Study Population

Eligible patients were male or female, were aged 40 years or older, had stable moderate to very severe COPD (forced expiratory volume in 1 second [FEV_1]/forced vital capacity <0.70 and FEV_1 <70% predicted[1]), and had a smoking history of at least 10 pack-years. Predicted values of lung function were based on sex, height, and self-reported race and ethnicity (based on fixed categories).[15] Patients were required to have at least 1 of the following: cerebrovascular disease (eg, stroke or transient ischemic attack, carotid stenosis), coronary artery disease (myocardial infarction, angina, angioplasty/stent/coronary artery bypass graft), or peripheral vascular disease (history of claudication). Alternatively, patients could have at least 2 atherothrombotic risk factors, including age 65 years or older for men and 70 years or older for women, waist circumference 40 inches or more for men and 38 inches or more for women, estimated glomerular filtration rate less than 60 mL/min and microalbuminuria (30-300 mg albumin per 24 hours or 30-300 μg albumin per 1 mg creatinine on a spot urine test), dyslipidemia, diabetes, or hypertension. Patients could continue background treatment, with the exception of anticholinergics (LAMAs and SAMAs), which were not permitted.

Patients were excluded if they were taking triple therapy (inhaled corticosteroid [ICS], LAMA, and long-acting β_2-agonist [LABA]), had unstable or life-threatening COPD or cardiovascular disease, had a lung disease other than COPD, had planned lung transplantation or lung surgery, or had a malignancy treated within 5 years before screening. Initially, patients were required to have had at least 1 treated COPD exacerbation in the year prior to screening but were excluded if an exacerbation occurred within 4 weeks of screening.[14] To enhance recruitment, the requirement of a prior exacerbation was removed after approximately 50% of patients (n = 1734) were enrolled to increase accrual and allow for a broader patient population.[14] At the same time, the upper limit of FEV_1 was increased from 70% to 80% predicted.

Outcome Measures

The primary safety outcome was “on-study” time to first adjudicated MACE (ie, irrespective of treatment exposure; with MACE defined as cardiovascular death, nonfatal myocardial

infarction, or nonfatal stroke). The primary efficacy outcome measure was the annual rate of moderate to severe COPD exacerbations during the first year of the study while taking the study drug ("on-treatment" time). This time frame was selected because it was expected that almost all nondiscontinued patients would have completed 1 year of treatment by the time that at least 122 patients experienced an adjudicated MACE.[14] Exacerbations were defined as increased COPD symptoms lasting 2 days or longer and required treatment with antibiotics and/or systemic corticosteroids or led to hospitalization or death. The study was not designed with co-primary end points; therefore, a positive result on risk of MACE would be interpreted as such regardless of the outcome on exacerbations. However, following a negative result for MACE, the results for efficacy would be exploratory only.

A secondary safety analysis was performed of risk of MACE that also included other serious cardiovascular events (eg, acute heart failure or life-threatening arrhythmias). Exacerbations that required hospitalization were analyzed as a secondary efficacy outcome.

Sensitivity analyses were performed to include exacerbations that occurred during the first year of follow-up, regardless of whether patients were taking the study treatment. In addition, the time to first MACE was analyzed with an "on-treatment" approach (ie, among patients actively taking study treatment) as a sensitivity analysis of the primary safety analysis.

Exploratory efficacy analyses included subgroup annual rates of moderate to severe COPD exacerbations, including patients taking an ICS (including ICS-LABA treatment) at baseline. Individual MACE components were also examined.

An exploratory safety outcome measure was all-cause mortality, analyzed at the time of the common closeout date or 3-year follow-up (vital status was ascertained approximately every 3 months for the first 2 years and once every 6 months during year 3).

Treatment-emergent adverse events, serious adverse events, and adverse events leading to discontinuation were recorded.

To account for the multisite design of the study, a frailty analysis incorporating site as a covariate was performed as a post hoc sensitivity analysis to determine whether 1 or more sites had an undue influence on the results.

Adjudication of MACE

Members of a clinical event committee, consisting of 2 cardiologists and 1 pulmonologist, provided an independent, blinded medical review and adjudication of all MACE and other cardiovascular events of interest. Potential events were adjudicated using a consistent and prespecified set of criteria defined in the clinical event committee's charter, which was based on the 2014 draft Clinical Data Interchange Standards Consortium guidance[16]; discrepancies among reviewers were resolved by a consensus of the committee.

Statistical Analysis

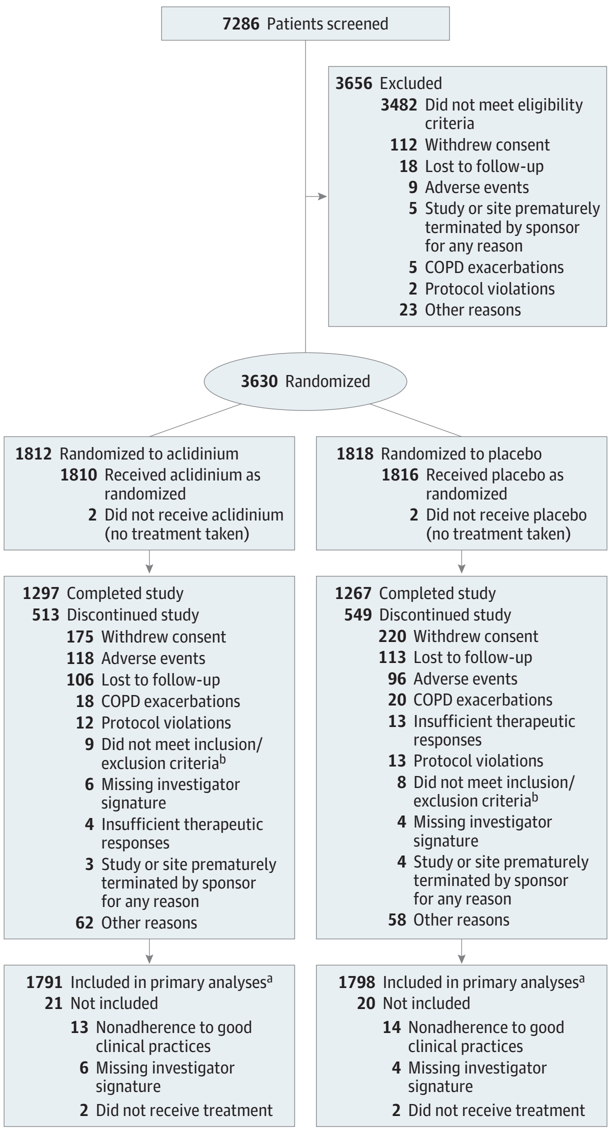
All analyses were prespecified. The trial was powered on the 3-year safety outcome, with the 1-year efficacy outcome nested as a separate end point within the overall trial. The study was designed such that at least 122 patients having a MACE would achieve 90% power to rule out a hazard ratio (HR) of 1.8 comparing time to first MACE for aclidinium vs placebo. Statistical noninferiority was concluded if the 1-sided 97.5% CI was less than 1.8. The noninferiority margin of 1.8 was based on the US Food and Drug Administration's guidance for establishing the cardiovascular safety for marketing of diabetes drugs.[17] The initially projected accrual of 4000 patients needed to acquire 122 patients with MACE provided 89% power to detect a 1-year on-treatment 14% reduction in exacerbation rate at α=.05, assuming an exacerbation rate of 0.81 per patient-year and 30% discontinuation rate of study treatment. The 14% reduction in exacerbation rate was based on data from the UPLIFT trial.[6]

Time to first MACE was analyzed using a Cox proportional hazards model with baseline cardiovascular risk group (prior events and risk factors), smoking status, and treatment group as covariates. The assumption of proportional hazards was supported by inspection of log-cumulative hazard plots. Chronic obstructive pulmonary disease exacerbation rates were analyzed using negative binomial regression with treatment group, and baseline ICS use, baseline COPD severity, smoking status, and 1-year exacerbation history as factors. The study was powered for overall MACE but not for the individual components, which were analyzed in an exploratory fashion only. The frailty model included site as a frailty term with a log-normal distribution.

Safety and efficacy analyses were conducted on the full analysis set (all patients who took at least 1 dose of treatment). The primary safety analysis was based on randomized treatment assignment irrespective of treatment discontinuation ("on-study" analysis). A sensitivity analysis of MACE that occurred while patients were taking study treatment (until the time of study drug discontinuation) used windows of 0 and 15 days after stopping treatment.

The primary efficacy analysis was an on-treatment analysis during the first year of treatment, excluding events that occurred after treatment discontinuation. An on-study sensitivity analysis included exacerbations that occurred during the first year of the study regardless of treatment discontinuation. Prespecified subgroups were analyzed based on age, sex, race, smoking status, baseline ICS use (including ICS-LABA treatment), baseline COPD severity, and history of COPD exacerbations in the year prior to baseline visit. Subgroup differences were inferred based on tests of treatment × subgroup interaction. Efficacy end points were tested sequentially in a hierarchical manner; ie, the secondary analysis of the primary efficacy end point (rate of moderate to severe COPD exacerbations; on-study analysis) was tested only when the primary analysis (rate of moderate to severe COPD exacerbations; on-treatment analysis) achieved statistical significance and the secondary efficacy end point (exacerbations that required hospitalization; on-treatment analysis) was tested only when both primary and secondary analyses of the primary efficacy end point (rate of moderate to severe COPD exacerbations; on-treatment and on-study analyses) achieved statistical significance.

Figure 1. Patient Flow in the ASCENT-COPD Randomized Clinical Trial



COPD indicates chronic obstructive pulmonary disease.

[a] For safety outcomes, 70.7% of patients had completed the 3-year study or were currently enrolled in the study at the time the study was stopped; for efficacy outcomes, 67.3% of patients had completed 12 months of treatment or were in their first year of treatment when the study was stopped.

[b] Patients were randomized in error.

Otherwise, nominal *P* values were to be provided and interpreted descriptively. To assess the robustness to variations of the data assumptions underlying the primary analysis of the primary efficacy end point, several sensitivity analyses were conducted using jump-to-reference and copy reference approaches and tipping-point analysis.[18]

Various multiple imputation methods were used to address the effect of missing data assumptions in the analysis of the primary safety and efficacy variables (eAppendix in Supplement 1). All reported outputs were produced using SAS version 9.3 (SAS Institute Inc) in a secure, validated environment. The significance threshold was $P < .05$ for all end points.

Protocol Amendment

Approximately halfway through the study, the protocol was amended to increase accrual rates (eTables 1 and 2 in Supplement 1). As the study progressed, it was determined that many potential participants who met the requirement for prior COPD exacerbation were taking triple therapy; however, patients taking triple therapy were excluded from the trial to avoid switching patients from triple therapy to dual therapy should they be randomized to placebo. The protocol was subsequently amended to permit enrollment of high-risk patients who did not have an exacerbation history as well as other minor changes while maintaining the exclusion of patients taking triple therapy.[14]

Results

Patient Characteristics

The first patient was enrolled on October 16, 2013, and the last on August 22, 2016. The final patient completed follow-up on September 21, 2017. At study closeout, 3630 patients had been randomized; 1791 patients randomized to aclidinium and 1798 randomized to placebo were included in analyses and 41 patients overall were excluded (**Figure 1**). The treatment groups were well matched for clinical and demographic characteristics (**Table**); the patient population (mean age, 67.2 years) comprised mostly male patients (58.7%); former smokers (56.5%); and those with symptomatic disease (mean COPD assessment test score, 20.7 of 40, with higher scores indicating more symptoms), moderate to severe airflow limitation (85.3%), and 1 or more COPD exacerbations in the preceding year (60.1%). Inhaled corticosteroids were used by 56.8% of patients prior to the study, usually in combination with a LABA (51.2%) (Table). During the study, 64.2% of patients used an ICS, most frequently in combination with a LABA (59.4%) (eTable 3 in Supplement 1). At least 2 atherothrombotic risk factors were present in 95.9% of patients; 47.7% had a history of cardiovascular disease (eTable 4 in Supplement 1).

Overall, 67.3% of patients completed 12 months of treatment or were in their first year of treatment when the study was stopped; the median exposure time during the first year (on-treatment analysis) was 365 days for both aclidinium and placebo. In addition, 70.7% of patients had completed the 3-year study or were currently enrolled in the study at the time the study was stopped (Figure 1); the median exposure time (including time after treatment discontinuation) was 495 days for aclidinium and 478 days for placebo. Vital status at the end of the study was available for 1732 patients (96.7%) in the aclidinium group and 1725 (95.9%) in the placebo group. Patients whose vital status was missing were censored at their last study contact.

Primary Outcomes

The number of patients who experienced an adjudicated composite MACE was 69 (3.9%) in the aclidinium group vs 76 (4.2%) in the placebo group. The Cox regression HR was 0.89 (1-sided 97.5% CI, 0-1.23), which did not cross the prespecified

Table. Patient Demographics and Characteristics by Treatment Group

Characteristics	Aclidinium (n = 1791)	Placebo (n = 1798)
Age, mean (SD), y	67.1 (8.5)	67.2 (8.3)
Sex, No. (%)		
Male	1059 (59.1)	1046 (58.2)
Female	732 (40.9)	752 (41.8)
Race, No. (%)[a]		
White	1603 (89.5)	1650 (91.8)
Black or African American	165 (9.2)	138 (7.7)
Other[b]	23 (1.3)	10 (0.6)
Body mass index, mean (SD)[c]	29.7 (6.8)	29.5 (6.9)
Obese (≥30), No. (%)	771 (43.1)	739 (41.1)
Current smoker, No. (%)	784 (43.8)	778 (43.3)
COPD assessment test score, mean (SD)[d]	20.7 (7.3)	20.7 (7.2)
Postbronchodilator FEV_1 % predicted, mean (SD)	47.7 (14.9)	47.8 (15.2)
COPD severity, No. (%)		
Moderate (FEV_1 ≥50% to <80% predicted)	796 (44.4)	808 (44.9)
Severe (FEV_1 ≥30% to <50% predicted)	742 (41.4)	714 (39.7)
Very severe (FEV_1 <30% predicted)	220 (12.3)	244 (13.6)
COPD exacerbations in previous year, No. (%)[e]	1068 (59.6)	1088 (60.5)
No. of prior exacerbations, No. (%)		
0	723 (40.4)	710 (39.5)
1	786 (43.9)	810 (45.1)
≥2	282 (15.8)	278 (15.5)
COPD exacerbation rate in previous year, mean (SD)	0.8 (0.9)	0.8 (1.0)
Prior COPD-related medication, No. (%)[f]	1650 (92.1)	1678 (93.3)
SABA	1217 (68.0)	1249 (69.5)
LABA + ICS (fixed combination)	838 (46.8)	800 (44.5)
LAMA	217 (12.1)	247 (13.7)
Leukotriene inhibitor	150 (8.4)	127 (7.1)
SABA + SAMA	144 (8.0)	135 (7.5)
Oxygen	124 (6.9)	125 (7.0)
SAMA	89 (5.0)	89 (5.0)
Systemic corticosteroids	70 (3.9)	77 (4.3)
ICS	69 (3.9)	69 (3.8)
LABA + LAMA + ICS (free combination)	45 (2.5)	64 (3.6)
LABA + ICS (free combination)	36 (2.0)	52 (2.9)
LAMA + ICS (free combination)	33 (1.8)	31 (1.7)
LABA + LAMA (fixed combination)	29 (1.6)	30 (1.7)
Xanthines	29 (1.6)	30 (1.7)
LABA + LAMA (free combination)	24 (1.3)	14 (0.8)
LABA	19 (1.1)	26 (1.5)
Oral PDE4 inhibitor	19 (1.1)	24 (1.3)
Vaccines	5 (0.3)	10 (0.6)
Cromones	1 (0.1)	1 (0.1)
LABA + ICS fixed and LABA + LAMA fixed, separately	1 (0.1)	1 (0.1)
Monoclonal antibody	1 (0.1)	0

Abbreviations: COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; PDE4, phosphodiesterase type 4; SABA, short-acting β_2-agonist; SAMA, short-acting muscarinic antagonist.

[a] Self-reported.

[b] Includes Asian, Native Hawaiian or other Pacific Islander, American Indian or Alaska Native, and other races.

[c] Calculated as weight in kilograms divided by height in meters squared.

[d] Score range of 0 to 40 with higher scores indicating more symptoms; a score >10 indicates symptomatic COPD and >20 indicates a high disease impact.

[e] Defined as worsening of COPD symptoms (dyspnea, cough, sputum) for ≥2 consecutive days that required treatment with antibiotics and/or systemic corticosteroids or resulted in hospitalization or led to death.

[f] Prior treatments were not mutually exclusive. Fixed combinations were defined as >1 drug in a single device; free combinations used multiple individual devices. Data included in fixed or free combinations do not appear in monotherapy categories. For prior medications that were stopped before randomization and concomitant medications that were taken before randomization and continued beyond the first dose of treatment, see eTable 3 in Supplement 1.

noninferiority margin of 1.8 (**Figure 2**). The annual rate of moderate to severe exacerbations during the first year of treatment was significantly lower in patients treated with aclidinium vs placebo by on-treatment analysis (aclidinium, 0.44; placebo, 0.57; rate ratio, 0.78; 2-sided 95% CI, 0.68-0.89; $P < .001$) (**Figure 3**A).

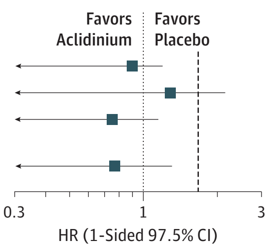
Secondary Outcomes

Because the primary objective was met, the secondary analyses were valid. The rate of COPD exacerbations requiring hospitalization was significantly reduced with aclidinium vs placebo in the on-treatment analysis (0.07 vs 0.10, respectively; rate ratio, 0.65; 2-sided 95% CI, 0.48-0.89; $P = .006$) (Figure 3A).

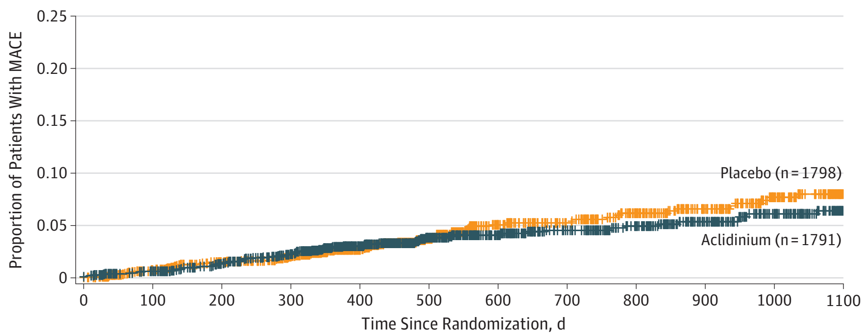
Figure 2. Risk of MACE and Time to First Adjudicated MACE (On-Study Analysis)

A Risk of MACE

	Aclidinium (n = 1791)		Placebo (n = 1798)		
	No. (%)	Patient-Years, No.	No. (%)	Patient-Years, No.	HR (1-Sided 97.5% CI)
MACE	69 (3.9)	2828.9	76 (4.2)	2748.1	0.89 (0-1.23)
Cardiovascular death	26 (1.5)	2863.7	19 (1.1)	2803.7	1.34 (0-2.42)
Nonfatal myocardial infarction	28 (1.6)	2876.5	38 (2.1)	2809.2	0.72 (0-1.18)
Nonfatal stroke	18 (1.0)	2888.1	24 (1.3)	2819.5	0.74 (0-1.36)



B Time to first adjudicated MACE



No. at risk												
Aclidinium	1791	1699	1593	1500	1144	834	662	572	503	423	349	201
Placebo	1798	1684	1578	1476	1100	805	604	538	465	400	321	183

HR indicates hazard ratio; MACE, major adverse cardiovascular event. Estimates of HRs and 1-sided 97.5% CIs comparing aclidinium with placebo were derived using the Cox proportional hazard model with treatment group, baseline cardiovascular severity, and smoking status as factors. Observations were censored for Kaplan-Meier curve. An HR >1.0 indicates higher risk of MACE with aclidinium and an HR <1.0, lower risk of MACE with aclidinium. The vertical dashed line indicates the margin of noninferiority, 1.8. The median exposure time (including time after treatment discontinuation) was 495 days (interquartile range, 369-893 days) for aclidinium and 478 days (interquartile range, 357-869 days) for placebo.

The secondary safety analysis, using an expanded definition of MACE comprising serious events of heart failure, arrhythmias, or cerebrovascular disease, yielded similar results, with events reported in 168 patients (9.4%) receiving aclidinium vs 160 (8.9%) receiving placebo (HR, 1.03; 1-sided 97.5% CI, 0-1.28) (eTable 5 in Supplement 1).

Sensitivity Analyses

The prespecified sensitivity analysis of time to first MACE using the on-treatment approach showed similar results to analysis using the on-study approach (eFigure 2 in Supplement 1). Sensitivity analyses of the annual rate of moderate to severe COPD exacerbations during the first year of treatment showed similar results using the on-study population (regardless of treatment status) (eFigure 3 in Supplement 1). An additional on-treatment analysis of time to first moderate to severe exacerbation in 574 patients in the aclidinium group (32.5%) and 631 (35.6%) in the placebo group who had events also supported this finding (HR, 0.82; 2-sided 95% CI, 0.73-0.92; $P < .001$) (Figure 3B). Subgroup analyses based on demographic and clinical characteristics showed a consistent treatment effect across all subgroups except among patients with FEV_1 greater than 50% predicted (comprising 45% of patients), who had fewer exacerbations and less relative benefit (P=.01 for interaction) (eFigure 4 in Supplement 1). The subgroup analysis also showed improvement in exacerbations both with and without baseline ICS use (including ICS-LABA use).

All-cause mortality was not significantly different between treatment groups (HR, 0.99; 2-sided 95% CI, 0.76-1.28) (eFigure 5 in Supplement 1).

Exploratory Outcomes

Among the components of MACE, nonfatal myocardial infarction (HR, 0.72; 1-sided 97.5% CI, 0-1.18), nonfatal stroke (HR, 0.74; 95% CI, 0-1.36), and cardiovascular death (HR, 1.34; 95% CI, 0-2.42) were also analyzed (Figure 2).

Adverse Events

Rates of treatment-emergent adverse events and serious adverse events were comparable between treatment groups (eTable 6 in Supplement 1). The most common treatment-emergent adverse events (occurring in ≥5% of patients) were pneumonia, urinary tract infection, and upper respiratory tract infection. The anticholinergic adverse effect of dry mouth was uncommon, occurring in 5 patients (0.3%) receiving aclidinium and 10 (0.6%) receiving placebo; urinary retention occurred in 7 patients (0.4%) in each treatment group. The most common serious adverse events (occurring in ≥1% of patients) were pneumonia, atrial fibrillation, congestive heart failure, and coronary artery disease.

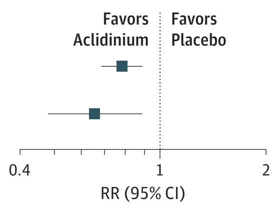
Post Hoc Analysis

Hazard ratio estimates from the on-study analysis of time to first MACE with site included as a frailty term did not

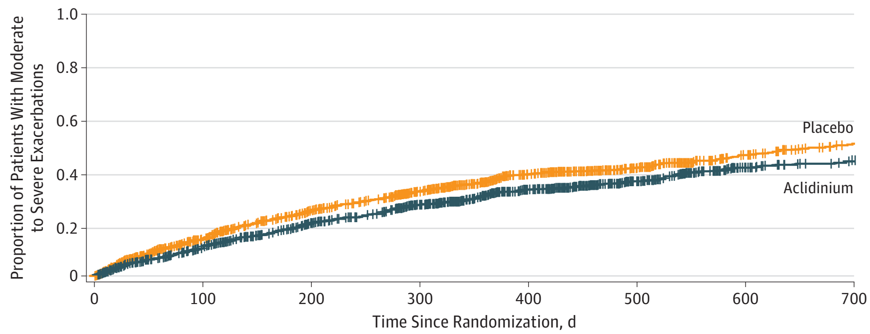
Figure 3. Moderate to Severe COPD Exacerbations During the First Year and Time to First Moderate to Severe Exacerbation (On-Treatment Analysis)

A Moderate to severe COPD exacerbations during first year

	Aclidinium (n = 1791)			Placebo (n = 1798)				
	No. of Events	Patient-Years, No.	Event Rate	No. of Events	Patient-Years, No.	Event Rate	RR (95% CI)	*P* Value
Moderate to severe exacerbations	644	1412.2	0.44	792	1363.4	0.57	0.78 (0.68-0.89)	<.001
Hospitalizations due to exacerbations	100	1412.2	0.07	144	1363.4	0.10	0.65 (0.48-0.89)	<.006



B Time to first moderate to severe COPD exacerbation



No. at risk								
Aclidinium	1791	1409	1134	929	607	383	240	201
Placebo	1798	1319	1022	820	509	322	205	165

COPD indicates chronic obstructive pulmonary disease; RR, rate ratio. A, Least-squares means from a negative binomial regression model, with treatment group, baseline inhaled corticosteroid use, baseline COPD severity, history of ≥1 exacerbation in the past 12 months, and smoking status as factors; the log of the exposure time adjusted for the time the patients experienced exacerbations was an offset variable. B, Cox regression analysis. Observations were censored for Kaplan-Meier curve. Log-rank *P* = .001 comparing aclidinium with placebo, stratified by baseline COPD severity and smoking status. There were 574 patients (32.5%) with events in the aclidinium group and 631 (35.6%) in the placebo group (hazard ratio, 0.82; 95% CI, 0.73-0.92; *P*<.001). Median observation time was 321 days (interquartile range, 121.5-365 days) for aclidinium and 283 days (interquartile range, 96-365 days) for placebo. A unique exacerbation was one that occurred 7 or more days after completion of treatment with corticosteroids or antibiotics for a previous event.

differ substantially from the primary analysis (eFigure 6 in Supplement 1).

Discussion

Among patients with COPD and increased cardiovascular risk, aclidinium compared with placebo did not result in an inferior risk of major cardiovascular events over 3 years, indicating no evidence of increased cardiovascular risk among patients receiving aclidinium vs placebo. The rate of moderate to severe COPD exacerbations was reduced over the first year.

No patient subgroup demonstrated a difference in efficacy except when analyzed by baseline COPD severity, in which the treatment benefit was observed only in patients with FEV_1 of 50% predicted or less. This may be explained by the lower exacerbation rate seen in the placebo group in patients with moderate airway obstruction vs severe or very severe obstruction. In addition, outcomes were similar regardless of on-study or on-treatment analysis. Patients who at baseline were taking an ICS or dual ICS-LABA treatment had a lower exacerbation rate with aclidinium vs placebo, and similar benefit was also present in those not taking an ICS or ICS-LABA. Thus, aclidinium decreased the exacerbation rate when added to background ICS or ICS-LABA treatment.

Outcomes of this trial add data to the long-standing controversy over the safety of LAMAs in COPD.[5-11] In general, observational studies have shown increased cardiovascular risk whereas placebo-controlled clinical trials have not shown increased cardiovascular risk.[7,19] This discrepancy has been attributed to the exclusion of patients with cardiovascular comorbidities and renal impairment in COPD clinical trials of LAMA therapy.[20,21] Consequently, this trial specifically enrolled patients with elevated cardiovascular risk and found no increase in cardiovascular risk with aclidinium. Furthermore, aclidinium was well tolerated, and the incidences of anticholinergic adverse events and atrial fibrillation were not increased vs placebo, although the study was not powered to evaluate these events. These findings extend the results of a pooled analysis (n = 2781) of 6 short-term randomized clinical trials in patients with moderate to severe COPD that found no evidence of increased cardiovascular risk with aclidinium vs placebo and a subanalysis of 1607 patients with cardiovascular risk factors that found no difference in the incidence of cardiovascular or cerebrovascular adverse events.[22] In contrast, 2 large case-control studies showed similar increases in risk for both LAMAs and LABAs within

30 days of treatment initiation, with a reduction in cardiovascular risk after 30 days.[19,23] One possibility is that the early observation of cardiac events with both classes of bronchodilators was the result of patients with new onset of chest symptoms receiving an incorrect diagnosis of worsening COPD symptoms, when the correct diagnosis was worsening cardiac symptoms. This trial cannot specifically address the concern regarding new-onset treatment because many patients were using a LAMA or LABA prior to screening.

Because patients with COPD exacerbations are at higher risk of subsequent MACE and all-cause mortality,[3,4,24-27] it might be hypothesized that the reduction in exacerbations seen with aclidinium might be reflected in a reduction in cardiovascular events or the exploratory outcome of all-cause mortality. However, consistent with a recent study of ICS-LABA treatment in patients with mild to moderate COPD and cardiovascular risk factors,[28] this was not seen in this trial. In addition, a recent post hoc study of tiotropium found no increased risk in patients with recent cardiovascular events; however, patients with unstable or acute cardiovascular disease were not enrolled in that study.[12]

This trial had several strengths. By enrolling patients with increased cardiovascular risk and continuing the study until an adequate number of adjudicated MACE had occurred, the study demonstrated that aclidinium was noninferior to placebo with respect to the risk of a new MACE. Furthermore, this trial is unique insofar as it was designed with an efficacy outcome nested within it, allowing for risk-benefit comparisons within the same study population.

Limitations

The study has several limitations. It was not powered for cause-specific mortality, and a numerically increased point estimate for cardiac death with aclidinium was observed. However, the number of events was small and the confidence intervals were wide. Accordingly, the possibility that there was an increase in cardiac deaths cannot be excluded. However, there was no difference between treatments in the more reliable exploratory outcome of all-cause mortality, and the point estimates of the other MACE components tended to be lower with aclidinium. In addition, the study used a LAMA with a low potential for systemic effect,[29] as reflected by low reported rates of dry mouth and urinary retention; this finding should therefore be extrapolated cautiously.

Conclusions

Among patients with COPD and increased cardiovascular risk, aclidinium was noninferior to placebo for risk of MACE over 3 years. The rate of moderate to severe exacerbations was reduced over the first year.

ARTICLE INFORMATION

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Author Contributions: Dr Wise had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Wise, Chapman, Scirica, Zetterstrand, Reisner, Garcia Gil.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Wise, Chapman, Garcia Gil.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Daoud, Zetterstrand, Garcia Gil.
Administrative, technical, or material support: Wise, Chapman, Daoud, Reisner.
Supervision: Wise, Scirica, Daoud, Reisner, Garcia Gil.

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